



CLINICAL REPORT

Recognition and Management of Iatrogenically Induced Opioid Dependence and Withdrawal in Children

abstract

FREE

Opioids are often prescribed to children for pain relief related to procedures, acute injuries, and chronic conditions. Round-the-clock dosing of opioids can produce opioid dependence within 5 days. According to a 2001 Consensus Paper from the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine, dependence is defined as “a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.” Although the experience of many children undergoing iatrogenically induced withdrawal may be mild or goes unreported, there is currently no guidance for recognition or management of withdrawal for this population. Guidance on this subject is available only for adults and primarily for adults with substance use disorders. The guideline will summarize existing literature and provide readers with information currently not available in any single source specific for this vulnerable pediatric population. *Pediatrics* 2014;133:152–155

INTRODUCTION

Opioids are commonly prescribed to children of all ages.¹ Primarily, they are used in short duration for pain related to either a procedure or an acute injury. Utilization of opioids in these circumstances is widely accepted and generally considered low risk. Even in this circumstance, it is important to realize that children prescribed opioids for as little as 7 days can develop opioid dependence and exhibit drug-specific withdrawal symptoms on abrupt discontinuation of medications. Children in ICU settings are especially prone to these issues, because they are often exposed to opioids for longer periods of time when they have ongoing pain or require long-term sedation/analgesia as part of their care.

To understand the consequences of opioid use, it is important that one understands some basic definitions related to opioid use and adaptation to this use. The most commonly accepted definitions for these behaviors are based on a 2001 Consensus Paper from the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine.² The definitions are as follows:

Jeffrey Galinkin, MD, FAAP, Jeffrey Lee Koh, MD, FAAP,
COMMITTEE ON DRUGS, and SECTION ON ANESTHESIOLOGY
AND PAIN MEDICINE

KEY WORDS

opioids, dependence, withdrawal, sedation, analgesia

This document is copyrighted and is property of the American Academy of Pediatrics and its Board of Directors. All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. The American Academy of Pediatrics has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-3398

doi:10.1542/peds.2013-3398

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2014 by the American Academy of Pediatrics

- Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
- Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

The consensus paper also noted, "most specialists in pain medicine and addiction agree that patients treated with prolonged opioid therapy do develop physical dependence and sometimes tolerance, but do not usually develop addictive disorders."

Although the experience of many children undergoing iatrogenically induced withdrawal may be mild or go unreported, there is currently no guidance for recognition or management of withdrawal for this population. (Guidance for newborn infants is available from the American Academy of Pediatrics.³) Guidance available on this subject is mostly from adults and primarily from literature on adults with substance use disorders. This clinical report summarizes existing literature on this subject and provides readers with information currently not available in any single source specific for this vulnerable pediatric population. The scope of this document is limited to children who received opioid medications outside the neonatal and infant period.

EPIDEMIOLOGY OF OPIOID USE IN THE PEDIATRIC POPULATION

In 2009, approximately 7.2 million outpatient opioid prescriptions were dispensed for children in the United States.¹ The frequency of opioid prescriptions to children has doubled in the past decade.⁴ The vast majority of these prescriptions were written for children between the ages of 10 and 17 years, with many of these prescriptions for postprocedural and postoperative use.

BEHAVIORAL AND PHYSIOLOGIC CHARACTERISTICS OF OPIOID DEPENDENCE AND WITHDRAWAL

In most clinical situations, opioid dependence does not manifest any symptoms until opioid administration is abruptly decreased or discontinued (sometimes in favor of nonopioid analgesics), resulting in symptoms of withdrawal. Withdrawal also occurs when an alteration in gastrointestinal absorption leads to decreased absorption of oral opioid and a subsequent decrease in opioid blood concentration. Finally, transition from intravenous to oral administration is not always a predictable conversion, and withdrawal symptoms can occur when oral dosing results in a significantly lower blood concentration of opioid than the previous intravenous dosing. The signs and symptoms associated with withdrawal in the pediatric population can vary somewhat by age but are relatively consistent overall.^{5,6}

Behavioral changes are often the primary manifestation of withdrawal and include anxiety, agitation, insomnia, and tremors. In addition to behavioral symptoms, physiologic changes commonly seen in withdrawal include increased muscle tone, nausea, vomiting, diarrhea, decreased appetite, tachypnea, tachycardia, fever, sweating, and hypertension. Care must be taken to

rule out other causes of these symptoms, such as infection and sepsis.

Many of these symptoms are assessed in tools used to monitor children undergoing potential opioid withdrawal.⁵ Specific scales for children include the Modified Narcotic Abstinence Scale, the Sedation Withdrawal Score, the Sophia Observation Withdrawal Symptoms Scale, and the Opioid Benzodiazepine Withdrawal Scale. Of these pediatric-specific scales, only the Sophia Observation Withdrawal Symptoms Scale has been validated.⁷ The only validated scales to measure withdrawal in adults are the Clinical Opiate Withdrawal Scale (an 11-item clinician-administered scale assessing opioid withdrawal) and the Clinical Institute Narcotic Assessment scale, but these are not specific for children.⁸ Consistently using and becoming familiar with any of these scales (adult or pediatric) will allow a clinician a means of detecting early signs of withdrawal so a treatment strategy can be implemented. Clinicians should also interpret results from the use of these scales within the clinical context of each individual patient, because there may be reasons other than opioid withdrawal that could explain certain behaviors being scored.

MANAGEMENT STRATEGIES FOR APPROPRIATE WEANING OF OPIOIDS AND TREATMENT OF WITHDRAWAL SYMPTOMS

Prevention is the preferred approach to management of opioid withdrawal symptoms and is achieved by decreasing the dose of opioid over time rather than abruptly discontinuing the medication, commonly referred to as "weaning." When discontinuing an opioid, the first step is to decide whether a patient is at risk for opioid withdrawal. Opioid withdrawal symptoms have been reported in as little as 5 days,⁶ but there seems to be

considerable interpatient variability. Most patients who have received an opioid for less than 7 days do not suffer from withdrawal and can have their medication discontinued quickly. Patients who have been exposed to an opioid for longer than 14 days will usually need to follow a weaning protocol to prevent withdrawal symptoms. Those patients with opioid exposure lasting between 7 and 14 days may need to be weaned off their opioid but usually can be weaned more quickly than those with exposure longer than 14 days. It is critical to assess a patient's pain status at the time of anticipated weaning. A patient should not have ongoing painful stimuli or a condition that requires continuation or escalation of opioid dose to adequately manage pain before weaning. After it is determined that a patient should be weaned from an opioid, a weaning protocol is developed taking into account the length of opioid exposure and total daily opioid dose. Unfortunately, there is no clear outcome-based evidence to support an ideal weaning protocol, but it does seem logical that individual patient response to weaning is more important than following a rigid schedule. It is beyond the scope of this article to prescribe specific guidelines; the generally accepted approach involves transition to a longer-acting opioid formulation, such as methadone, extended-release morphine, or extended-release oxycodone (this is an off-label use for these drugs). Once the patient is stabilized on the long-acting opioid, weaning is usually accomplished by steps of a 10% to 20% decrease in the original dose every 24 to 48 hours.⁶ During opioid weaning, parents and care providers should carefully monitor for signs of withdrawal. If withdrawal symptoms are observed, the planned dose of opioid, from the weaning schedule, should be administered, and administration of

additional rescue opioid should be considered if withdrawal symptoms are severe. A shorter-acting opioid should be available for signs of withdrawal, painful procedures, or for breakthrough pain. Adjunctive medications, such as clonidine, gabapentin, and dexmedetomidine, have been used⁶ to decrease withdrawal symptoms and to help in the opioid-weaning process. These drugs are not labeled for this indication, and there is little information, other than the articles referenced in this clinical report, to provide guidance on their use.

Another common clinical scenario in patients with opioid dependence is concomitant long-term benzodiazepine exposure. Again, there are no clear guidelines for the concurrent weaning of benzodiazepines and opioids. It would seem prudent to have patients wean from 1 medication at a time rather than attempt to wean from both at the same time. This way, any signs of withdrawal can be more clearly attributed to 1 medication.

There is little in the literature describing the use of behavioral strategies for management of iatrogenic opioid withdrawal symptoms in children and adolescents. However, there are reports of the successful use of these interventions for the management of benzodiazepine withdrawal in adult patients with insomnia.^{9,10} Behavioral intervention has also been used as part of treatment programs in adolescents who are dependent on either prescription opioids or heroin.¹¹ Given the success of multidisciplinary pain management interventions that include some form of behavioral therapy, it would seem logical that behavioral intervention would be a useful part of any weaning program to help with sleep hygiene, anxiety/mood symptoms, and pain-related symptoms that may occur during the weaning period.

Overall, the management of opioid dependence and tolerance can be managed safely and comfortably for most patients. The most common difficulties in the process are using a weaning schedule that is too rapid or not understanding that the patient's weaning protocol may not provide adequate analgesia if there are ongoing (or new) painful stimuli.

CONCLUSIONS

There is a high prevalence in the use of prescription opioids in the pediatric population (see the earlier section "Epidemiology of Opioid Use in the Pediatric Population") for durations exceeding 1 week. It is essential to realize that abrupt discontinuation of opioids can lead to drug-specific withdrawal symptoms. For patients receiving prolonged opioid therapy, it is best to develop strategies in conjunction with the patient's care team and family to minimize withdrawal symptoms while following a set opioid-weaning strategy. Understanding opioid withdrawal is key to its prevention. Research in this field is just beginning and should be looked at as a priority, because the frequency of prescribed opioid use in children has doubled in the past decade.⁴

LEAD AUTHORS

Jeffrey L. Galinkin, MD, FAAP
Jeffrey Lee Koh, MD, FAAP

COMMITTEE ON DRUGS, 2012–2013

Daniel A. C. Frattarelli, MD, FAAP, Chairperson
Jeffrey L. Galinkin, MD, FAAP
Thomas P. Green, MD, FAAP
Timothy D. Johnson, DO, MMM, FAAP
Kathleen A. Neville, MD, FAAP
Ian M. Paul, MD, MSc, FAAP
John N. Van Den Anker, MD, PhD, FAAP

LIAISONS

John J. Alexander, MD, FAAP – *Food and Drug Administration*
James D. Goldberg, MD – *American College of Obstetricians and Gynecologists*
Janet D. Cragan, MD, MPH, FAAP – *Centers for Disease Control and Prevention*

Michael J. Rieder, MD, FAAP – *Canadian Pediatric Society*
 Adelaide S. Robb, MD – *American Academy of Child and Adolescent Psychiatry*
 Hari Sachs, MD, FAAP – *Food and Drug Administration*
 Anne Zajicek, MD, PharmD, FAAP – *National Institutes of Health*

STAFF

Tamar Haro, JD
 Mark Del Monte, JD
 Raymond J. Koterak, MHA

SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE EXECUTIVE COMMITTEE, 2012–2013

Carolyn Fleming Bannister, MD, FAAP, Chairperson
 Joseph D. Tobias, MD, FAAP, Chairperson-elect
 Corrie T. M. Anderson, MD, FAAP
 Kenneth R. Goldschneider, MD, FAAP
 Courtney A. Hardy, MD, FAAP

FORMER EXECUTIVE COMMITTEE MEMBERS

Constance Houck, MD, FAAP – Immediate Past Chairperson

Jeffrey Lee Koh, MD, FAAP
 David Mark Polaner, MD, FAAP

LIAISONS

Jeffrey L. Galinkin, MD, FAAP – *American Academy of Pediatrics Committee on Drugs*
 Mark Singleton, MD, FAAP – *American Society of Anesthesiologists Committee on Pediatrics*

STAFF

Jennifer Riefe

REFERENCES

1. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305(13):1299–1301
2. American Academy of Pain Medicine; American Pain Society; American Society of Addiction Medicine. *Definitions Related to the Use of Opioids for the Treatment of Pain*. Glenview, IL, and Chevy Chase, MD: American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine; 2001
3. Hudak ML, Tan RC; American Academy of Pediatrics Committee on Drugs; Committee on Fetus and Newborn. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2). Available at: www.pediatrics.org/cgi/content/full/129/2/e540
4. Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. *Pediatrics*. 2010;126(6):1108–1116
5. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. *Crit Care Med*. 2008;36(8):2427–2432
6. Anand KJ, Willson DF, Berger J, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics*. 2010;125(5). Available at: www.pediatrics.org/cgi/content/full/125/5/e1208
7. Ista E, de Hoog M, Tibboel D, Duivenvoorden HJ, van Dijk M. Psychometric evaluation of the Sophia observation withdrawal symptoms scale in critically ill children. *Pediatr Crit Care Med*. 2013;14(8):761–769
8. Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. *Drug Alcohol Depend*. 2009;105(1–2):154–159
9. Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry*. 2004;161(2):332–342
10. Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Grégoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ*. 2003;169(10):1015–1020
11. Motamed M, Marsch LA, Solhkhah R, Bickel WK, Badger GJ. Differences in treatment outcomes between prescription opioid-dependent and heroin-dependent adolescents. *J Addict Med*. 2008;2(3):158–164